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STETINA BRUNDA GARRED & BRUCKER 75 ENTERPRISE, SUITE 250 ALISO VIEJO, CA 92656			TUNGATURTHI, PARITHOSH K	
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DATE MAILED: 09/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/759,828	Applicant(s) SMITH ET AL.	
	Examiner Parithosh K. Tungaturthi	Art Unit 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-17 is/are pending in the application.
 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-17 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date ____. | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

1. Claims 1-17 are under examination.

Claim Objections

2. Claims 2-11 are objected to because of the following informalities: The instant claims are objected to for reciting "According to claim 1....", instead the claims should recite "A process according to claim 1...".

Claims 6-17 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim can only be written in an alternative form. See MPEP § 608.01(n).

Claims 6-11 are objected to for reciting "according to claim 1-5.." because a claim is an improper multiple dependent claim.

Claims 12-15 are further objected to for being an improper multiple dependent claim for reciting "according to claims 1-6 a process.....", because claims 1-6 are already improper multiple dependent claims.

Accordingly, appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-17 are vague and indefinite for reciting "a process of immunotherapy that utilizes a succession of antitumor antibodies....". It is not clear what the applicant means by "a process of immunotherapy". For the purposes of this office action, it is interpreted as "a method of treatment". Further, it is unclear by what the applicant means by "utilizes a succession of antitumor antibodies". It is interpreted as "a method comprising administering a succession of antitumor antibodies". Thus, claim 1 and the further dependent claims are interpreted as "a method of treatment comprising administering a succession of antitumor antibodies prepared from different species".

Claim 1 is further unclear because it recites "..... antibodies prepared from different species". What does the applicant mean by ".... prepared from different species"? Does the applicant mean that the antibodies are from a different species than the patient? As written, it is not clear for one skilled in the art to determine the metes and bounds of the claims.

Claim 3 recites the limitation "tumor antigen" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Further, claim 3 is indefinite for reciting "tumor antigen includes all types of antigen found in tumors including those shared by normal cells such as material released by dead tumor cells into the surrounding environment". It is unclear as to what the applicant means by "tumor associated antigens", "cluster determinants markers" and

Art Unit: 1643

"intracellular components". What "tumor associated antigens", "cluster determinants markers" or the "intracellular components" is the applicant referring to? As written, it is impossible to determine the metes and bounds of the claims.

Claim 4 is indefinite for not further limiting claim 1. Claim 1 recites "...succession of antitumor antibodies..." and claim 4 recites "...antitumor antibody includes all types of polyclonal and monoclonal antibodies..." which is not further limiting from the antibodies of claim 1. Appropriate correction is required.

Claim 5 is unclear for reciting "according to claim 5...". The claim is not clear because it depends on itself. For the purposes of this office action, it is interpreted as "the process according to claim 1...". In addition, claim 5 is unclear for reciting "may consist of". What does the applicant mean by "may consist of"? Does the applicant mean that the process of treatment of claim 1 consists of one of the antibodies as listed in claim 5 (whole IgG OR whole IgM OR Fab OR F(ab)₂)? Appropriate correction is required.

Claims 7-11 are unclear for reciting "utilizing a variety of linked to carrier antibodies.....". What does the applicant mean by a variety of agents are linked to the carrier antibodies? Is there a specific agent (such as a radionuclide, anti-cancer drugs, toxin, etc.) that is linked to a specific antibody OR is any antibody linked to any of the agents randomly? As written, it is impossible to determine the metes and bounds of the claims. Appropriate correction is required.

Art Unit: 1643

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

MPEP § 2164.01 states:

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to

Art Unit: 1643

practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

In the instant case, the claims are broadly drawn to a method of treatment comprising administering a succession of antitumor antibodies prepared from different species, wherein the species of animals used to prepare the antitumor antibodies include: horse, donkey, cow, goat, sheep, rabbit, turkey, chicken, rat, mice and other animal species including human autoantibodies, wherein the term "tumor antigen" includes all types of antigen found in tumors including those shared by normal cells such as tumor associated antigens, cluster determinant (CD) markers, and intracellular components such as nuclear and cytoplasmic material released by dead tumor cells into the surrounding environment, wherein the term "antitumor antibody" includes all types of polyclonal and monoclonal antibodies, wherein the antitumor antibodies may consist of the whole IgG molecule or the whole IgM molecule or the binding Fab and F(ab)₂ fragments of the antibody, wherein the cancer patient is pre-tested by laboratory testing and by skin testing against the species animal immunoglobulin to determine non-reactivity before treatment with the antitumor antibody. The claims are also drawn to a process of cancer treatment utilizing a therapeutic dosage of a variety of radionuclides linked to carrier antitumor antibodies from different species which is injected into the cancer patient, further utilizing a variety of cytotoxic anti-cancer drugs linked to carrier antitumor antibodies from different species which is injected into the cancer patient, further utilizing a variety of biological response modifiers linked to carrier antitumor antibodies which is injected into the cancer patient, further utilizing a variety of toxins

linked to carrier antitumor antibodies which is injected into the cancer patient, further utilizing a variety of blood vessel growth inhibiting compounds linked to carrier antitumor antibodies which is injected into the cancer patient, whereby the cancer patient receives a single pharmaceutical linked to different species antibodies directed against a specific antigen, whereby the cancer patient receives a single pharmaceutical linked to different species antibodies directed against multiple antigens, whereby the cancer patient receives different pharmaceuticals linked to different species antibodies directed against a specific antigen, whereby the cancer patient receives different pharmaceuticals linked to different species antibodies directed against multiple antigens, whereby the cancer patient receives a pre-targeting injection of antitumor antibody from one animal species, followed by later injections of radionuclide labeled antibody and/or drug labeled antibody prepared in a different species and directed against the immunoglobulin component of the first animal species and whereby the cancer patient is only exposed once to the antibody from a particular animal species which minimizes the risk of the patient developing an allergic reaction to the therapeutic antibodies.

The specification only teaches a Carrier Antibody against a Single Cancer Antigen Prepared in Different Species and Labeled with One Type of Anti-Cancer Pharmaceutical (example 1, in particular); Carrier Antibody against a Single Cancer Antigen Prepared in Different Species and Labeled with Different Types of Anti-Cancer Pharmaceuticals (example 2, in particular); Carrier Antibodies against Multiple Tumor Antigens Prepared in Different Species and Labeled with One Type of Anti-Cancer Pharmaceutical (example 3, in particular) and Carrier Antibodies against Multiple

disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

Thus, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to treat cancer comprising administering a succession of antitumor antibodies prepared from different species; yet, defining a substance by its principal biological activity amounts to an alleged conception having no more specificity than that of a wish to know the identity of any material with that biological property. See *Colbert v. Lofdahl*, 21 USPQ2d 1068, 1071 (BPAI 1991).

The position of the Office is further substantiated by the teachings of Kelland (*Eur. J. Cancer*. 2004 Apr; **40** (6): 827-836). Kelland has reviewed the reliability of the model in predicting clinical response; see entire document (e.g., the abstract). While the successful use of such models in cytotoxic drug development is conclusive, Kelland discloses that today there is far less focus on the development of such drugs (page 833, column 2); rather, the focus is upon the development of "molecularly-targeted", largely cytostatic drugs, such as those disclosed in the instant application, which may act in synergy with other drugs to selectively reduce or inhibit the growth of neoplastic cells (e.g., page 885). In particular, where such drugs are naked humanized antibodies that act through mechanisms such as ADCC, Kelland states the models are of limited value, because such mechanisms depend upon the recruitment of the host's (i.e., mouse)

immune response, which differs from or is not reflective of that found in man (page 834, column 2). With such limitations of the xenograft model in mind, Kelland suggests that the case for using the model within a target-driven drug development cascade need to be justified on a case-by-case basis (page 835, column 1). Still, Kelland et al. does not altogether discount the usefulness of such models, since, at present, "it is premature and too much a 'leap of faith' to jump directly from *in vitro* activity testing (or even in silico methods) to Phase I clinical trials (via preclinical regulatory toxicology)" (page 835, column 2). Kelland, however, does not advocate the use of a single xenograft model to exhort one to accept assertions of the effectiveness of treating multiple and different diseases using the same agent, as has been done in the instant application, since Kelland compels one to decide on a case-by-case basis whether such a model is suitable or not.

Gura (Science. 1997, 278:1041-1042) teaches that although researchers had hoped that xenografts would prove to better models for studying cancer in humans and screening candidate therapeutic agents for use in treating patient diagnosed with cancer, "the results of xenograft screening turned out to be not much better than those obtained with the original models". Gura states that as a result of their efforts, " '[w]e had basically discovered compounds that were good mouse drugs rather than good human drugs' ".

Further, Peterson et al. (European J Cancer, 2004, 40:837-844) teaches numerous agents have show exciting activity in preclinical models and yet have had minimal activity clinically; see, e.g., the abstract. Such disappointments, Peterson et al.

Art Unit: 1643

Cancer Antigens Prepared in Different Species and Labeled with Different Types of Anti-Cancer Pharmaceuticals (example 4, in particular). The specification does not provide any information as to the treatment of cancer comprising administering a succession of antitumor antibodies prepared from different species. The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation. Thus, relating to the claimed invention, there is no information in the specification.

As such, the specification is viewed merely as an invitation to one skilled in the art to develop the claimed invention. As the court stated in:

As we stated in *Genentech*:

Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

See *Genentech*, 108 F.3d at 1366, 42 USPQ2d at 1005. We thus conclude that the district court did not clearly err in finding that the specifications provided little guidance or direction as to the practice of antisense in cells other than *E. coli*, and that such minimal disclosure as there was constituted no more than a plan or invitation to practice antisense in those cells.

Id. at 1138. Here, however, the specification provides comparably little disclosure, failing to disclose any guidance, direction, or working examples.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling

discloses, “have led to reasonable skepticism about the true value of both syngeneic and xenograft rodent tumour models in accurately identifying agents that will have important clinical utility” (abstract). Peterson et al. reviews the limitations of the xenograft models; see entire document (e.g., page 840, column 2).

Schuh (*Toxicologic Pathology*. 2004; **32** (Suppl. 1): 53-66) reviews the trials, tribulations and trends in tumor modeling in mice to disclose, for example, that “[c]ommon reliance on survival and tumor burden data in a single mouse model often skews expectations towards high remission and cure results; a finding seldom duplicated in clinical trials” (abstract). Furthermore, Schuh discloses, “[d]espite historical significance and ongoing utility, tumor models in mice used for preclinical therapeutic intervention often error towards false positive results and curing cancer in mice” (page 62, column 1). Given the noted limitations of xenograft models, Schuh suggests that testing in tumor-bearing animals may help to improve the predictive value of animal modeling; see entire document (e.g., the abstract).

Bibby (*Eur. J. Cancer*. 2004 Apr; **40** (6): 852-857) teaches that in the interest of finding more clinically relevant models, orthotopic models have been developed; see entire document (e.g., the abstract). In such “orthotopic” models, treatment is initiated after removal of the primary tumor and distant metastases are well established and macroscopic. These models have their advantages, but the procedures involved in using such models are far more difficult and time-consuming than conventional subcutaneous (e.g., xenograft) models; see, e.g., page 855, column 2.

The problem with accepting such an assertion lies in the fact that the data generated using such mouse models cannot be reasonably extrapolated to reliably and accurately predict whether the claimed invention can be used to attenuate at least a substantial number of pathoangiogenic conditions comprising cancer and furthermore, as of yet, the clinical, therapeutic application of cancer vaccines to attenuate cancer has been met with very little success. In addition to references cited above, which describe such disappointing results and attribute the lack of success to various differences, such as the poor extrapolation of promising preclinical data to predict clinical efficacy, Wang et al. (*Exp. Opin. Biol. Ther.* 2001; 1 (2): 277-290) reviews the state of the art of T-cell-directed cancer vaccines for treatment of melanoma and states:

Saved for scattered reports, however, the success of these approaches has been limited and T-cell-directed vaccination against cancer remains at a paradoxical standstill whereby anticancer immunization can be induced but is not sufficient, in most cases, to induce tumour regression (abstract).

Wang et al. further states:

Among the questions raised by this paradoxical observation [that systemic T-cell responses to vaccines often do not lead to objective clinical tumor regression] stands the enigma of whether tumour resistance to immunotherapy is due to insufficient immune response or because tumour cells rapidly adapt to immune pressure by switching into less immunogenic phenotypes [citations omitted].

In addition, Hosono et al (*Br J Cancer* 1992, 65:197-200) teach that Human anti-murine antibody (HAMA) response is a serious problem in the repeated infusion of murine monoclonal antibodies (MoAbs). Hosono et al teach show that HAMA positive sera from seven patients with colorectal cancer, pancreas cancer, malignant melanoma or myocardial infarction who had previously received radiolabeled MoAbs consisted of

immune complexes composed of HAMA and MoAbs (please see the entire article, in particular). Hosono et al also teach that HAMA was composed of Ab responsive to Fc portion and/or CH1 or CL region of murine IgG. To support the above teachings, Roehrig et al (Annals of the New York Academy of Sciences. 2001. 951: 286-297) teach that using murine MAbs to modify human disease results in a human antimouse antibody (HAMA) response that eventually limits the effectiveness of subsequent murine antibody applications and that to reduce the HAMA response and make these MAbs more generally useful for humans, murine MAbs can be "humanized" or human MAbs with analogous reactivities can be developed (please see the entire article, in particular).

Further, Saijo et al. (*Cancer Sci.* 2004 Oct; 95 (10): 772-776) recently reviewed the reasons for negative phase III trial of molecular-target-based drugs and their combinations; see entire document (e.g., the abstract). Saijo et al. discloses that while numerous phase III trials have been conducted upon the basis of promising preclinical data such as that disclosed in the instant application, few have yielded strongly positive results, and the majority of results have been negative (e.g., abstract). Saijo et al. discloses that there are problems in preclinical prediction of combined effects of anticancer drugs, and the results of preclinical prediction of combined effects have been very poor (page 773, column 2). Saijo et al. teaches many reasons for the poor predictability of combined effects (page 774, Table 6).

Ferrari et al. (*Clin. Exp. Immunol.* 2003; **132**: 1-8), for examples, addresses the immunological hurdles to lung gene therapy, which continue to hinder the successful

Art Unit: 1643

clinical application of such treatments and yet which have not been resolved by the instant disclosure; see entire document (e.g., the abstract). Ferrari et al. teaches that although gene transfer to the lung is feasible, gene expression from both viral and non-viral vectors has been inefficient and inflammatory, antibody, and T cell responses limit transgene expression duration and re-administration (abstract), just as earlier published references also indicate. So, despite advancements in the art of gene therapy, the same limitations that hindered its successful therapeutic application in past years continue to hamper its clinical use today.

Thus, taken collectively, there is a preponderance of factual evidence of record that the showing provided in the supporting disclosure would not enable the skilled artisan to practice the claimed invention without undue experimentation, as required under the provisions of 35 U.S.C. § 112, first paragraph.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Conclusion

5. No claims are allowed


Art Unit: 1643

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Parithosh K. Tungaturthi whose telephone number is 571-272-8789. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

7. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
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LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER